[0029] Also provided herein a polynucleotide encoding the fusion protein as described above. Further provided is an expression vector comprising such a polynucleotide operably linked to a promoter, for example, a constitutive promoter, a tissue specific promoter, or an inducible promoter. The promoter may be a small molecule ligand-inducible two polypeptide ecdysone receptor-based gene switch promoter. The vector may be an adenoviral vector.

[0030] Further provided herein is a pharmaceutical composition comprising: the fusion protein as described above or a polynucleotide encoding the same; and a pharmaceutically-acceptable excipient. In certain embodiments, the polynucleotide may be contained in an expression vector.

[0031] Also provided is a method of treating cancer, the method comprising contacting a cell with the fusion protein as described above or a polynucleotide encoding the same. In embodiments wherein the cell is contacted with a polynucleotide, the polynucleotide may be contained in an expression vector and the cell contacted with the vector. In certain embodiments the cell is a cancer cell. In certain embodiments, the cell is a mammalian cell. In certain embodiments, the mammalian cell is an immune cell. In certain embodiments, the immune cell is a T cell.

[0032] Further provided is a method of treating cancer in a subject in need of such treatment, the method comprising administering the aforementioned composition comprising the fusion protein to a subject. In certain embodiments, the cancer is a refractory cancer. In certain embodiments, the subject is non-responsive to a treatment with an anti-PD-1 antibody or a CTLA-4 antibody. In certain embodiments, the method further comprises administering one or more additional anti-cancer agent, for example a PD-1 inhibitor (e.g., an anti-PD-1 antibody, or a fragment or variant thereof), PD-L1 inhibitor, and/or a CTLA-4 inhibitor (e.g., an anti-CTLA-4 antibody or a fragment or variant thereof). In certain embodiments, the method further comprises administering a cytokine, for example a fusion protein comprising IL-15 and IL-15Rα. In certain embodiments, the subject is a mammalian subject, for example a human. In certain embodiments, the cancer is mesothelioma, glioblastoma, endometrial cancer, colorectal cancer, gastric cancer, cervical cancer, ovarian cancer, pancreatic cancer, prostate cancer, breast cancer, stomach cancer, bladder cancer, liver cancer, Hodgkin's lymphoma, lung cancer, skin cancer, renal cancer, head and neck cancer, melanoma, bronchus cancer, urinary tract cancer, anal cancer, brain cancer, esophageal cancer, cervical cancer, uterine cancer, cancer of the oral cavity or pharynx, kidney cancer, testicular cancer, biliary tract cancer, small bowel cancer, appendix cancer, salivary gland cancer, thyroid gland cancer, adrenal gland cancer, osteosarcoma, chondrosarcoma, or a cancer of a hematological tissue. In certain embodiments, the cancer is cutaneous squamous-cell carcinoma, melanoma or basal cell cancer. In certain embodiments, the cancer is non-small cell lung cancer (NSLC) or small cell lung cancer (SCLC). In certain embodiments, the cancer is triple negative breast cancer (TNBC).

[0033] In certain embodiments, the method further comprises administering an effective amount of T cells engineered to express an exogenous receptor. In certain embodiments, the exogenous receptor is a chimeric antigen receptor, for example one that comprises an antigen binding domain that binds to an epitope on CD19, BCMA, CD23, BAFF-R, GPRC5D, CD44, CAIX, CD5, CD30, CD70, CD44v6, CD44v7, CD44v8, CD174, CD28, CD128, CD138, CS1, CLL-1, L1-CAM, FAP, ROR1, CEA, EGP-2, EGP-40, HER2, HER3, Folate-binding Protein, GD2, GD3, IL-13R-a2, IL-11Rα, EphA2, CSPG4, KDR, EDB-F, mesothelin, CD22, EGFR, Folate receptor α, MUC-1, MUC-4, MUC-16, MAGE-A1, h5T4, PSMA, PSCA, GPC3, c-met, TAG-72, EGFR, CD20, EGFRvIII, CD123, or VEGF-R2. In certain embodiments, the chimeric antigen receptor is an engineered T-cell receptor. In certain embodiments, the chimeric antigen receptor comprises an antigen binding domain comprising a sequence that is at least 90% identical to any one of SEQ ID NOs: 37-56. In certain embodiments, the chimeric antigen receptor comprises an antigen binding domain comprising a sequence that is at least 90% identical to SEQ ID NO: 35 or 36. In certain embodiments, the effective amount of engineered T-cells is at least 10^2 cells/kg, at least 10^4 cells/kg, or at least 10^5 cells/kg. In certain embodiments, the engineered T-cells further express a cytokine, for example a fusion protein comprising IL-15 and IL-15Rα.

[0034] Also provided is a use of a fusion protein of the present invention, or a polynucleotide encoding the same, in the manufacture of a medicament for use in the treatment of cancer.

BRIEF DESCRIPTION OF THE DRAWINGS

[0035] The features of the present disclosure are set forth with particularity in the appended claims. A better understanding of the features and advantages of the present disclosure will be obtained by reference to the following detailed description that sets forth illustrative embodiments, in which the principles of the disclosure are utilized, and the accompanying drawings of which:

[0036] FIG. **1** is a schematic of PD-1/PD-L1 in immunosuppression.

[0037] FIG. **2** is a schematic of TGF-3 in immunosuppression.

[0038] FIG. **3** shows TGF-β associated gene cluster correlated with metastatic disease and poor prognosis in subset of ovarian cancer patients (enriched in Stage III/IV).

[0039] FIG. **4**A, FIG. **4**B, and FIG. **4**C show a schematic design of antibody-TGFRII fusion protein design. In other exemplary embodiments, ADA2 can be fused to the antibody.

[0040] FIG. **5** is a graph showing blockade of PD-1/PD-L1 interaction by anti-PD-1 (VH6-VL5) IgG1-TGFβRII and anti-PD-1 (VH6-VL5) IgG4-TGFβRII.

[0041] FIG. **6** is a graph showing neutralization of TGF-β isoform signaling by anti-PD-1 (VH6-VL5) IgG1-TGFβRII and anti-PD-1 (VH6-VL5) IgG4-TGFβRII.

[0042] FIG. **7** is a graph showing neutralization of TGF-β2 isoform by anti-PD-1(VH6-VL5) IgG1-TGFβRII and anti-PD-1(VH6-VL5) IgG4-TGFβRII.

[0043] FIG. **8** is a graph showing neutralization of TGF-β3 isoform signaling by anti-PD-1(VH6-VL5) IgG1-TGFβRII and anti-PD-1(VH6-VL5) IgG4-TGFβRII.

[0044] FIG. **9**A, FIG. **9**B, and FIG. **9**C are graphs showing enhanced proliferation and IFN-γ production by stimulated PBMCs in the presence of anti-PD-1-TGFRII fusion protein in a dose dependent manner compared to anti-PD-1 or control antibodies.

[0045] FIG. **9**D and FIG. **9**E are graphs showing PD-1 receptor occupancy on $CD8^+$ T cells and IFN-γ production respectively when anti-PD-1-TGFRII fusion protein is